Patent
45198.00013.RCE(CIP1)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Erion *et al.*	
Serial No.: 09/518,501	Group Art Unit: 1624
Filed: March 3, 2000	Examiner: McKenzie, T.
Title: NOVEL PHOSPHORUS-CONTAINING PRODRUGS	

Commissioner for Patents
P.O. Box 1450
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DECLARATION OF JOHN C. CHABALA PURSUANT TO 37 C.F.R. § 1.132

I, John C. Chabala, a citizen of the United States, declare and say that:

1. I am an organic and medicinal chemist and hold a B.S. degree in chemistry from Bucknell University and a Ph.D. degree in organic chemistry from the Massachusetts Institute of Technology. I was employed by the Merck Sharp & Dohme Research Laboratories from 1975 to 1991 and was Executive Director of Basic Chemistry there from 1989 to 1991. From 1991 to 1992 I was Vice President, Central Chemistry and from 1992 to 1993 I was Vice President of Discovery Chemistry at Bristol-Myers Squibb. From 1993 to 1996 I was President and from 1993 to 1997 Chief Scientific Officer of Pharmacopeia, Inc. Currently, I am an independent consultant in medicinal chemistry to 12 biotechnology companies, two non-profit organizations, and two venture capital investment companies.

2. I have carried out research into pharmaceutical agents for cardiovascular diseases, central nervous system disorders, endocrine diseases, oncology, immunology and inflammation, metabolic diseases, and anti-infectives, as well as vaccines and veterinary products for over 28 years. I have also supervised natural products chemistry and macromolecular structure programs. I have authored over 40 scientific articles and have co-invented over 20 patents.

3. I have supervised the establishment and operation of high throughput screens using coupled enzymatic reactions, filtration techniques, antibody recognition, and fluorescence enhancement and quenching employing a variety of detection methods including spectrophotometry (both absorption and emission) and radioactivity measurement for four years. I have been awarded the

CERTIFICATE OF TRANSMISSION
(37 C.F.R. §1.8)

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being facsimile transmitted to the United States Patent and Trademark Office on the date shown below.

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Thomas Alva Edison Award from the Research and Development Council of New Jersey in 1987 and the New Jersey Institute of Chemistry Award in 1992. I am a member of the editorial board of the journal Molecular Diversity, have served as a member of the American Chemical Society Long Range Planning Committee and Predoctoral Fellowship Selection Committee, and have organized several sessions at national and international symposia. My Curriculum Vitae is attached as Exhibit A.

4. I am a paid consultant for Metabasis Therapeutics. I have reviewed the pending claims in this case, the specification, the priority applications, and the Office Action mailed June 16, 2003.

5. It is my understanding from the Office Action that the Examiner finds the term "M is selected from the group that attached to PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ or $P(O)(NHR^6)O^-$ is a biologically active agent but is not an FBPase inhibitor, and is attached to the phosphorus in formula I via a carbon, oxygen, sulfur or nitrogen atom" to be indefinite, not enabled, and lacking written description. In particular, I believe the Examiner is contending that one would not understand what a "biologically active agent" is, be able to determine the structure of M, know what compounds are included by the claims, and know how to make compounds of the invention. I believe these rejections apply to claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173.

6. Contrary to the Examiner's position, a person of ordinary skill in the art would have understood what was claimed as of March 5, 1999. As a medicinal chemist reading claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173, I clearly understand how to determine which compounds would be included and excluded by the claims. I believe that persons of ordinary skill in the art would also know how to determine whether a compound is within or outside the scope of the claims. The tests for whether a compound is or is not a biologically active agent that is not an FBPase inhibitor of this invention, do not require undue experimentation, and were well-known in the art as of March 5, 1999.

7. As a medicinal chemist, I understand the term "biologically active agent." In addition, I believe a person of ordinary skill in the art would be guided by the specification, which defines the term "biologically active agent" at pp. 21-22. The practicing medicinal chemist recognizes that the effect can be exerted on any component or sets of components of a living organism either within the complete organism or as separated components, such as its constitutive molecules, organelles, cells, tissues, organs, up to and including the complete organism.

8. I am aware that there are at least 300 patents issued from 1976 to the present that use the term "biologically active agent" in the claims. In general, the term "biologically active agent" is not defined in the specification in these patents. (*see e.g.*, U.S. Patent Nos. 6,602,975; 6,264,990; 5,980,551; 5,855,608; 5,783,211; 5,462,990; 5,028,424; 4,976,968; 4,704,942; and 3,975,350). I believe that this supports my conclusion that the term "biologically active agent" is well understood by a person of ordinary skill in the art.

9. By March, 1999, it was a matter of routine testing to determine whether or not a given compound is a biologically active agent that is not an FBPase inhibitor. The specification at p.21 indicates that an FBPase inhibitor is a compound that inhibits the human enzyme fructose-1,6-

bisphosphatase with an IC50 of at least 100 μM and lower glucose in a normal 18-hour fasted rat following a 100 mg/kg dose i.v. Simple spectrophotometric assays can be used to determine enzymatic activity. Such assays were well-known in March 1999.

10. High Throughput Screening enables rapid evaluation of large numbers of compounds (1000s per day). As of March, 1999, such screens were widely employed. For instance, a spectrophotometric enzymatic assay would have been and is easily employed in high throughput screening.

11. Given the guidance in the specification and the routine nature of the testing involved, one can easily determine what compounds fall within the scope of the claims with routine experimentation. Once a compound has been identified as a compound of the invention, as of March, 1999, a person of ordinary skill in the art could determine its purity and confirm its structure by routine liquid chromatography coupled directly to mass spectrometry as was and is commonly done.

12. The specification at pp. 89-98 clearly provides guidance on how to make compounds of the invention. A person of ordinary skill in the art could easily prepare compounds of the invention given the guidance in the specification and by employing other well-known reactions. In general, one is starting with a known MH and allowing it to react to form a phosphoramidate or one is starting with a known MPO_3^{2-} and converting it to a phosphoramidate. Such reactions are routine.

13. Additionally, as a medicinal chemist reading this Application, I would conclude that the inventors had possession of the claimed invention of claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173. I believe that persons of ordinary skill in the art would also conclude that the inventors had possession of the claimed invention of claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173.

14. I also understand that the Examiner has rejected claim 150 as indefinite because he contends that "no reactions are named and no conditions essential for any successful chemical reaction are specified."

15. A person of ordinary skill in the art understands how to transform a drug having a $-PO_3^{2-}$ or $-P(O)(NHR^6)O^-$ moiety into a compound of formula I by using straightforward and well-known reactions. The specification clearly provides guidance (starting at p. 103) on how to prepare prodrug compounds of this invention. The general procedure for phosphoramidate prodrugs begins with Example 1 and the general procedure for formation of nucleotide prodrugs begins with Example 4 on page 107.

16. I also understand that the Examiner has rejected claims 1-18, 20-46, 48-57, 150-153, 155-157, 165, and 171-173 as indefinite, lacking written description, and not enabled because of the use of the term "prodrug." In particular, it is my understanding that the Examiner finds the structures of the claimed prodrugs to be uncertain. The Examiner believes that one cannot determine what compounds are claimed.

17. Contrary to the Examiner's position, a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for whether a

compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 1999. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation.

18. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

December 15, 2003
Date

John C. Chabala, Ph.D.